

Human Gene Transfer Protocols Review by Institutional Biosafety Committees: Proposed Exemption for Low Biosafety Risk Protocols

**Jacqueline Corrigan-Curay, J.D. M.D.
Office of Biotechnology Activities
March 8, 2012**



Overview

- **Role of Institutional Biosafety Committees (IBCs) in review of human gene transfer (HGT) trials**
- **Feedback from some investigators**
- **Potential proposal for exemption of certain multisite, low biosafety risk gene transfer trials from IBC review**

Role of IBC Review in HGT Trials

- **Identify and manage biosafety issues raised by gene transfer agents**
 - Horizontal or vertical transmission risk
 - Safe handling and administration
 - Ensure that the informed consent incorporates information regarding risks that arise from the biological nature of the agent
 - Examine the preclinical animal data that support the safety of the vector
 - Identify new biosafety issues through analysis of adverse event reports
 - For protocols that undergo in-depth public review by the NIH Recombinant DNA Advisory Committee (RAC), ensure that the RAC recommendations are considered

Feedback from Some Investigators Regarding IBC Review of Multisite Trials

- A number of gene transfer clinical trials are conducted utilizing vectors for which there is considerable clinical experience and biosafety risks are well characterized**
- In such cases, multiple individual IBC reviews of low risk trials may add little benefit to protect public health and such reviews can be costly, e.g. setting up new IBCs, delays in initiating important research**
- A mechanism to streamline review of low biosafety risk trials is needed to facilitate research, especially for multisite trials**

Proposed Exemption from IBC Review for Certain Multisite Trials

- The multisite trial must use a plasmid or specified vectors derived from Risk Group 2 viruses that are not designed to integrate and are attenuated compared to the wild-type virus**
- There must be an initial safety trial with the specific vector and transgene that is comparable in terms of trial design and target population**

Vectors Eligible for Exemption from IBC Review (proposed)

After an initial safety trial is complete, gene transfer trials using plasmids or attenuated viral vectors that are not designed to integrate and are derived from specific RG2 viruses are eligible for exemption from IBC review. Viral vectors derived from the following viruses are eligible:

- Adenovirus
- HSV
- Poxviruses, except for vaccinia
- AAV*

* AAV vectors are not primarily designed to integrate and are more likely to remain episomal but integration does occur

Vectors Continued

- **Viral vectors eligible for exemption must be attenuated, i.e. shown to be less pathogenic compared to the wild type virus in both animal models and the previous clinical trial**
 - **Attenuation may be achieved by gene deletions or irreversible mutations in genes required for cell to cell transmission or virulence**

Multisite Trials Proposed for Exemption From IBC Review

- **Must use one of the specific vectors eligible for exemption.**
- **An initial safety study (e.g., Phase I trial) must have been completed. The multisite trial must use:**
 - **Same delivery method (e.g., data from an intratumoral administration study cannot be used to exempt an intravenous administration study).**
 - **Comparable concomitant interventions as in the initial safety trial (i.e., not proposing to test concurrent administration of new immunomodulatory agents with the gene transfer agent).**
 - **Same dose as tested in phase I trial.**

Proposal for Multisite Trials (cont....)

- The multisite trial's target population must be comparable to the safety study:
 - Age
 - If the multisite trial will enroll pediatric patients, the initial trial must have enrolled pediatric subjects at the dose to be tested.
 - Infectious disease burden
 - In addition to age, the working group recognized that the safety of an agent may differ if there are significantly different prevalence of chronic infectious disease, such as HIV, tuberculosis or malaria in the population studied.
- In the initial study there was no evidence of vertical or horizontal transmission of the agent.

Proposed Exemption from IBC review for Low Biosafety Risk Protocols

Has there been an initial safety trial in the same country?

NO

NOT ELIGIBLE FOR EXEMPTION.

YES

Does the trial use a plasmid, or attenuated viral vectors that are not designed to integrate and are derived from specific RG2 viruses: adenovirus, HSV, and poxviruses (except for vaccinia) or AAV (not primarily an integrating vector with a good safety history).

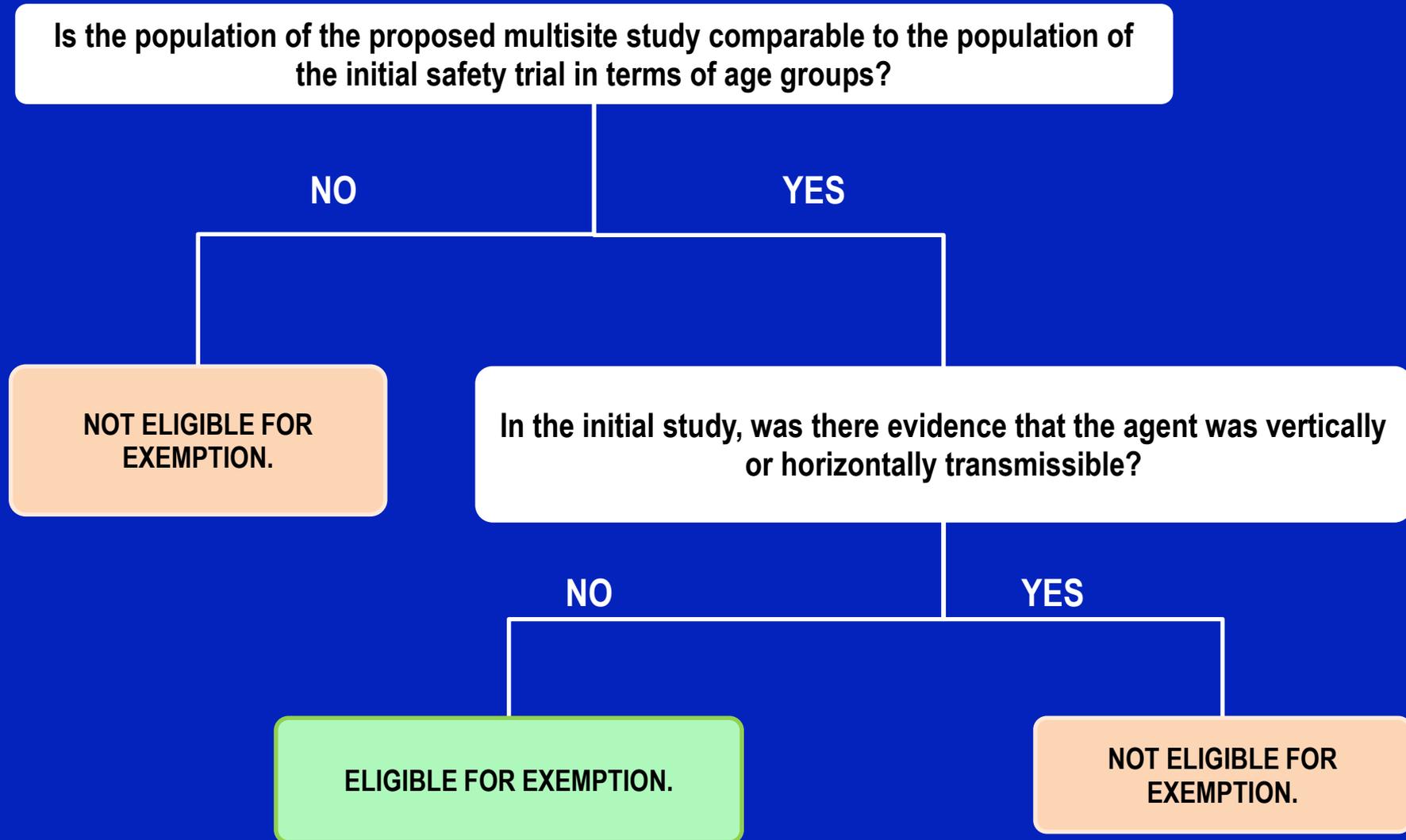
NO

NOT ELIGIBLE FOR EXEMPTION.

YES

Is the proposed multisite study design comparable to the initial safety study in delivery method, dosage, and concomitant interventions?

Proposed Exemption from IBC review for Low Biosafety Risk Protocols



Proposed IBC review of Exempt Trials

- **A decision that a trial meets the exemption criteria will be made by the IBC**
 - **At institutions that have an IBC, the PI should provide sufficient information for the IBC to determine that the trial does not require IBC review**
 - **A decision that the trial meets the criteria for exemption can be made by the BSO in consultation, as needed, with the IBC chair**
 - **An IBC can also decide to accept a decision made by another IBC regarding the exemption**
- **Institutions can always develop policies to review exempt protocols but that would be an institutional policy and not required under the Guidelines.**

Proposed IBC review of Exempt Trials, cont....

- **Once an IBC determines the trial is exempt from IBC review, there is no longer a requirement to set up an IBC at sites that do have an IBC (i.e. non-NIH funded sites).**
- **If the trial will enroll at sites in the US and outside the US but the safety study was conducted in the US only, the US sites can be exempt from review but the international site should have an initial IBC review in accordance with the local rules of that country or the NIH Guidelines.**

Proposed IBC review of Exempt Trials, cont....

- Trial sites for exempt protocols should be registered with OBA in accordance with the requirements of Appendix M-I-C-2, except that a copy of an IBC approval will not be required.
- The PI is still responsible for all reporting requirements under Appendix M, e.g. adverse event reporting, annual reports.
- While reporting to the IBC will not be required under the *NIH Guidelines*, institutions can establish their own reporting requirements in accordance with their policies.

Questions/Comments